Naval Medical Research Unit Dayton

Motion Sickness Countermeasures Laboratory

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Motion Sickness

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- Motion sickness (MS) is a problem across the services.

Motion Sickness

- 10-30% of United Kingdom naval crews experience seasickness during commonly experienced sea conditions.
  - In the worst conditions, this sickness incidence rises to 50-90%.

- From 1980-1992, the U.S. Navy Medical Information Management Center reported that 489, 266 new Naval recruits were diagnosed with MS and an additional 106, 932 revisits were documented.

Sources: Pethybridge, 1982; Dobie, 2000

Motion Sickness

- 10-38% of Student Naval Aviators and approx. 50% of Student Naval Flight Officers suffer from airsickness during training resulting in decreased flight performance ratings.
- Between Jan 09-Mar 14, 46.5% of Naval Aviation Safety Awareness Program (ASAP) reports indicated that at least some objectives were not met and/or performance was affected due to MS.
  - Numerous reports indicated that training flights were incomplete or returned to base early.
  - Approximately 22% of MS-related ASAP reports indicated that at least one individual became actively sick resulting in emesis.

Sources: Banks, Salisbury, & Ceresia, 1992; Dobie, 1974, Money, 1970; Simmons, Phillips, Lojewski, & Lawson, 2008

Motion Sickness

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- According to official Chief of Naval Air Training (CNATRA) records, between Oct 05-Aug 13, there were 5387 MS incident reports across 3 aviation training wings.
  - → approximately 57 MS incidents per month, 13 incidents per week, and 2 incidents per day.
  - 1248 incomplete training events → approx.13 incompletes per month and roughly 3 incompletes per week.
- 63% of all of the MS incidents were USN trainees.
- USMC trainees accounted for 22% of all MS incidents.

Motion Sickness

- In the Command and Control Vehicle, 55% of soldiers experienced moderate to severe MS.
  - MS symptoms not mitigated by short stops.
- Performance Decrements:
  - 46% in five of seven performance subtests
  - 83% in at least three subtests
  - 92% in at least two subtests.
- Performance degradation was comparable to blood alcohol level equivalencies equal to or greater than 0.08% (the legal limit in most states) in 35% of soldiers during movement and 22% during short halts.

Sources: Cowings, Toscano, DeRoshia, & Tauson, 1999; Hill & Tauson, 2005

Motion Sickness

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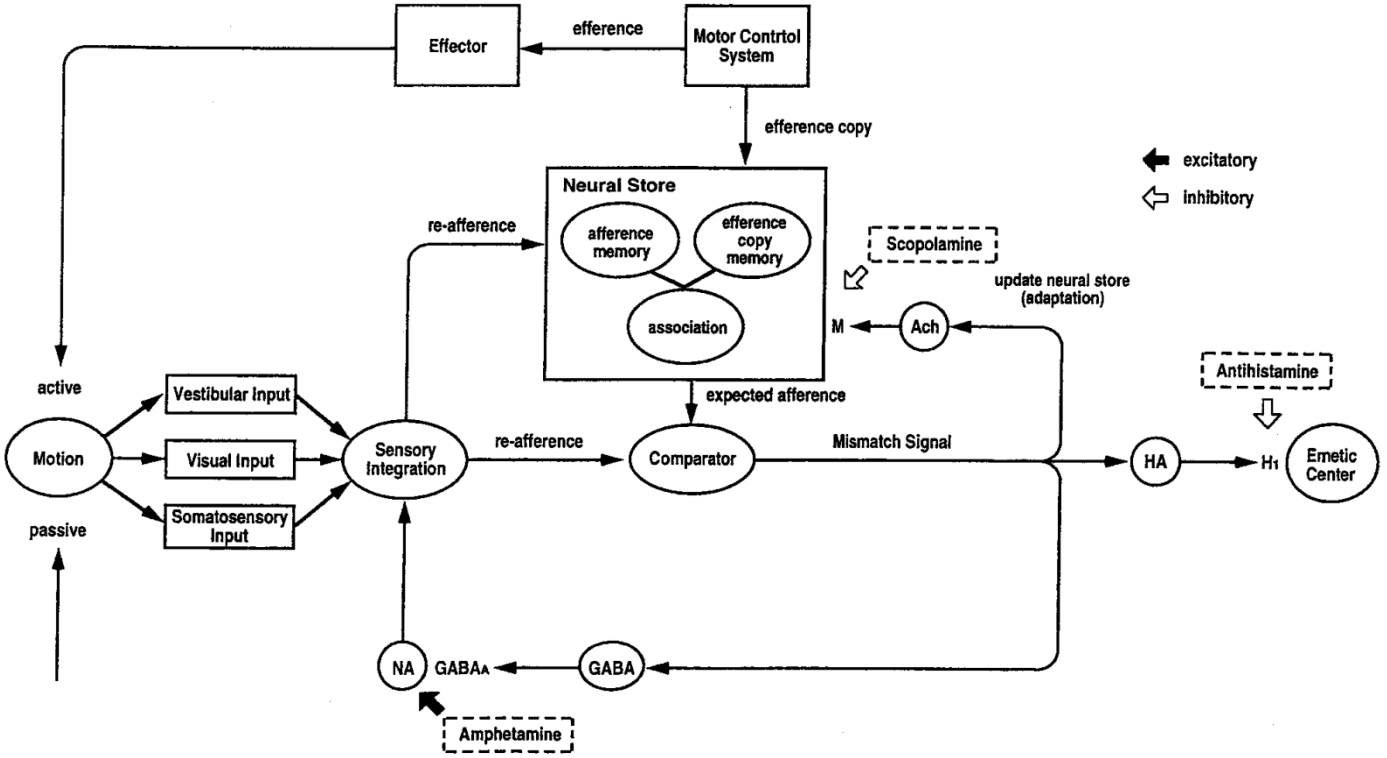
- Indirect vision driving of a HMMWV resulted in a 20-30% decrease in speed, 120-200% increase in driving errors, and 20% of drivers failed to successfully complete the task because of MS.
- In a modified M113 cognitive task, performance was 7-46% less accurate and 7-40% slower during moving operations.
- In a moving Amphibious Assault Vehicle, 74% of Marines reported moderate to severe MS symptoms.

Sources: Cowings, Toscano, DeRoshia, & Tauson, 1999; Hill & Tauson, 2005

Motion Sickness Etiology

- The exact etiology of motion sickness is unknown, but some of the major theories are:
  - Sensory Conflict Theory
  - Nystagmus Theory
  - Postural Instability Theory



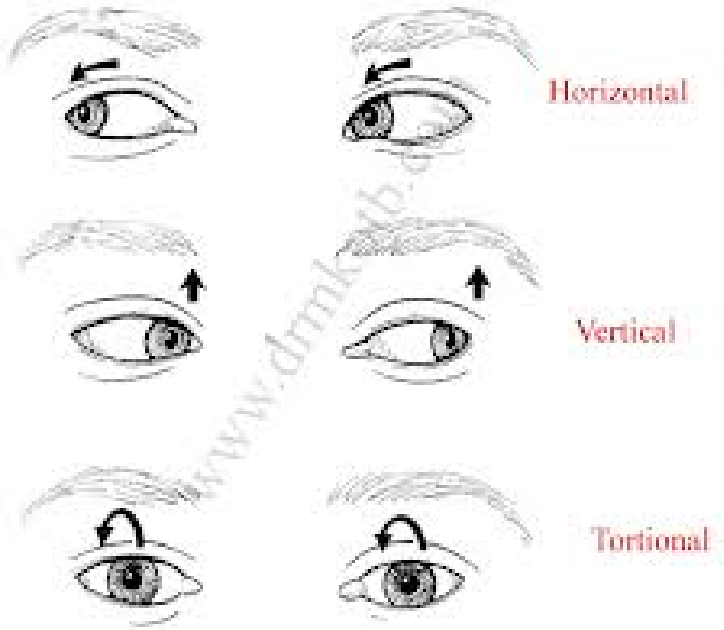
Source: Takeda, Morita, Horii, Nishiike, Kithara, & Uno, 2001

Motion Sickness Etiology

- Sensory Conflict Theory
  - MS originates from conflicting sensory input (vestibular, visual, and proprioceptive) that is generated as a result of unusual or provocative motion.
  - This conflicting sensory input “travels” from the peripheral vestibular and visual centers through the vestibular nuclei to a centrally located “comparator.”
  - If incoming sensory input conflicts with previously stored information, the comparator generates a mismatch signal response and the autonomic response of MS is induced.

Motion Sickness Etiology

- Nystagmus Theory
  - Certain stimuli can cause uncontrolled, rapid eye movements (nystagmus) which create such tension in the oculomotor muscle that the vagus nerve is stimulated, resulting in MS.

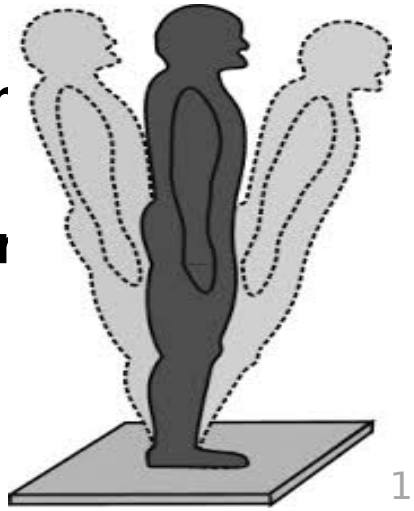


Types of Nystagmus

Motion Sickness Etiology

- Postural Instability Theory
  - Emphasis lies in the organism-environment interaction and the corresponding emergent behavior due to various organismal, environmental, and task constraints operating on the control of action.
  - Prolonged instability causes MS.
  - Thus, MS occurs in situations in which the individual does not possess or has not yet learned strategies for maintaining functionally effective postural control.

Key difference: The postural instability th
asserts that behavior (action) is a causal
of MS rather than being only a consequer



Motion Sickness Countermeasures

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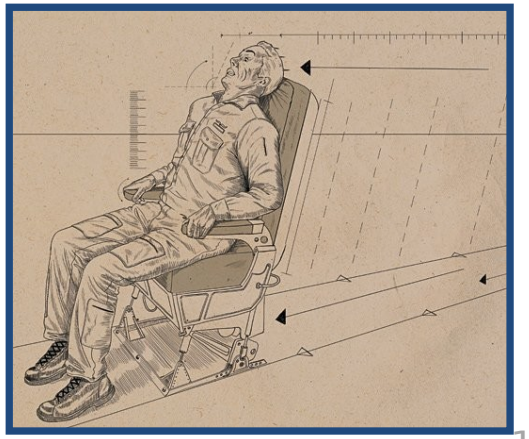
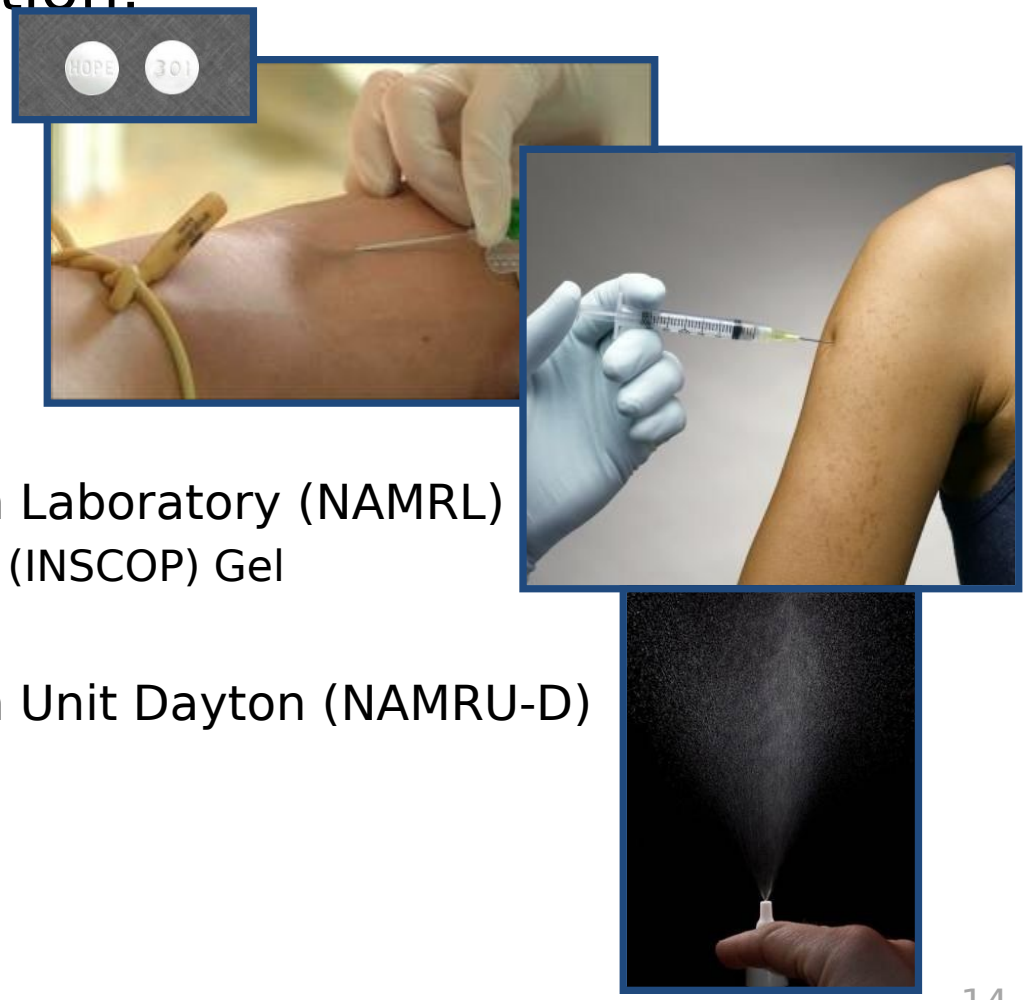
- Pharmacological
  - Antihistamines
    - Dramamine
    - Phenergan
  - Anticholinergics
    - Scopolamine
- Non-Pharmacological
  - Autogenic Feedback Training
  - Ginger
  - Pressure Point Bracelet
  - Repeated Exposure, Targeted Training



Different Routes of Administration

- Routes of Administration:
  - Oral Pill
  - Intramuscular Injection
  - Intravenous
  - Patch
  - Sublingual Spray
  - Intranasal Gel
    - Naval Medical Research Laboratory (NAMRL)
      - Intranasal Scopolamine (INSCOP) Gel
  - Intranasal Spray
    - Naval Medical Research Unit Dayton (NAMRU-D)
      - INSCOP Spray



NAMRU-D Study

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- Part 1: The Pharmacokinetic (PK) Phase
  - Purpose: Bioavailability & amount of scopolamine absorbed after 0.2 mg intranasal scopolamine (INSCOP) spray
    - Readings taken at regular intervals across 8 hours post-dose.
- Part 2: The Efficacy Phase
  - Purpose: Effectiveness, cognitive performance effects, & [illegible] profile of 0.2 mg INSCOP spray

Design

- Randomized, double blind, placebo controlled, cross over study
- Subjects
  - Active Duty Military
  - Motion Sickness Susceptibility Questionnaire (MSSQ
- PK Design
  - Goal: How does it absorb?
- Efficacy Design
  - Goal: Minimum effective dose / trade-off
- Stimulus
  - Rotary Chair
    - Neuro-Otologic Test Center (NOTC)
    - Active Coriolis cross-coupling

Cognitive Assessment

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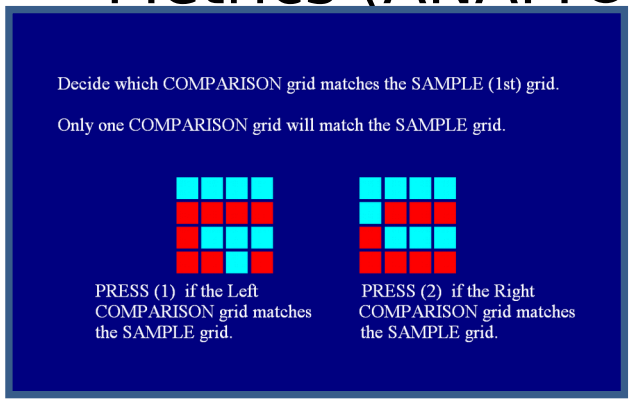
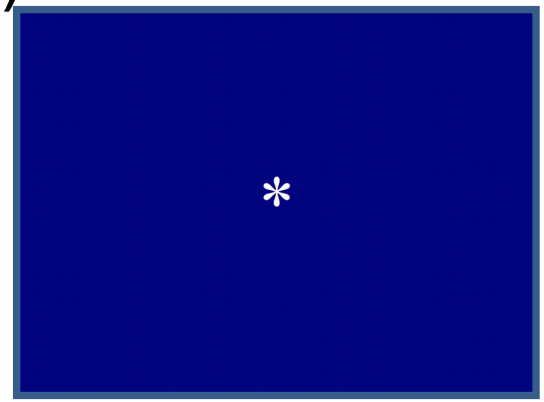
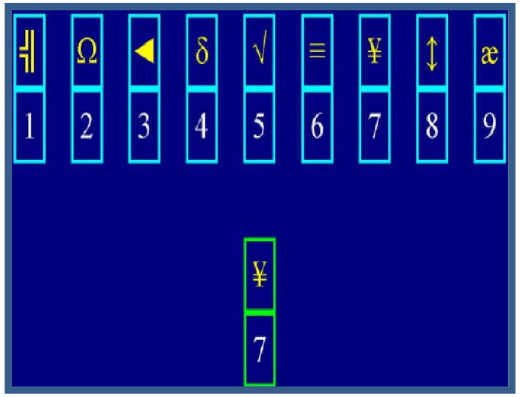
- Automated Neuropsychological Assessment Metrics (ANAM®)


Decide which COMPARISON grid matches the SAMPLE (1st) grid.
Only one COMPARISON grid will match the SAMPLE grid.
PRESS (1) if the Left COMPARISON grid matches the SAMPLE grid.
PRESS (2) if the Right COMPARISON grid matches the SAMPLE grid.

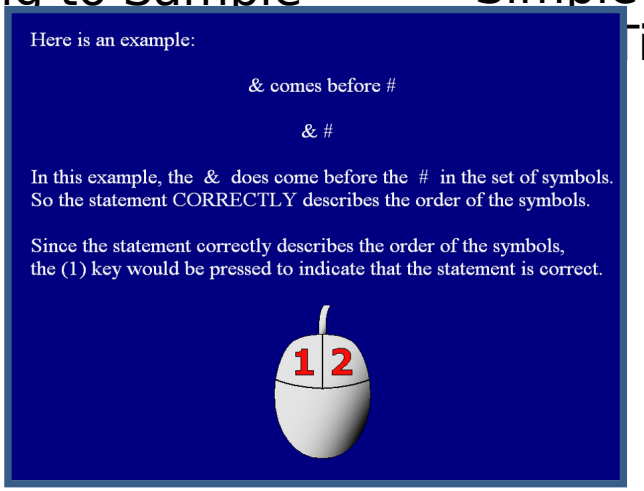
Matching to Sample



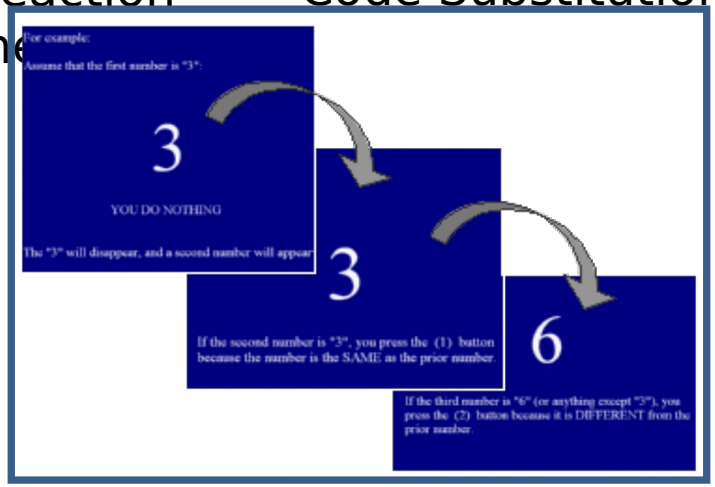
Simple Reaction Time



Code Substitution


Here is an example:
& comes before #
& #
In this example, the & does come before the # in the set of symbols. So the statement CORRECTLY describes the order of the symbols.
Since the statement correctly describes the order of the symbols, the (1) key would be pressed to indicate that the statement is correct.
1 2

Logical Reasoning


For example:
Assume that the first number is "3":
3
YOU DO NOTHING
The "3" will disappear, and a second number will appear.
3
If the second number is "3", you press the (1) button because the number is the SAME as the prior number.
6
If the third number is "6" (or anything except "3"), you press the (2) button because it is DIFFERENT from the prior number.

Running Memory

Dependent Variables

- Efficacy
  - Head Movements
- Biological Sampling
  - Blood Draws
  - Area Under the Curve (AUC)
  - C_{max}
- Subjective Assessment
  - Karolinska Sleepiness Scale (KSS)

- Cognitive Assessments
  - ANAM
  - Mean Reaction Time & Percent Correct
- Physiological Measures
  - Blood Pressure
  - Mean Arterial Pressure
  - Heart Rate
  - Temperature

Pilot Study Results: Systolic BP

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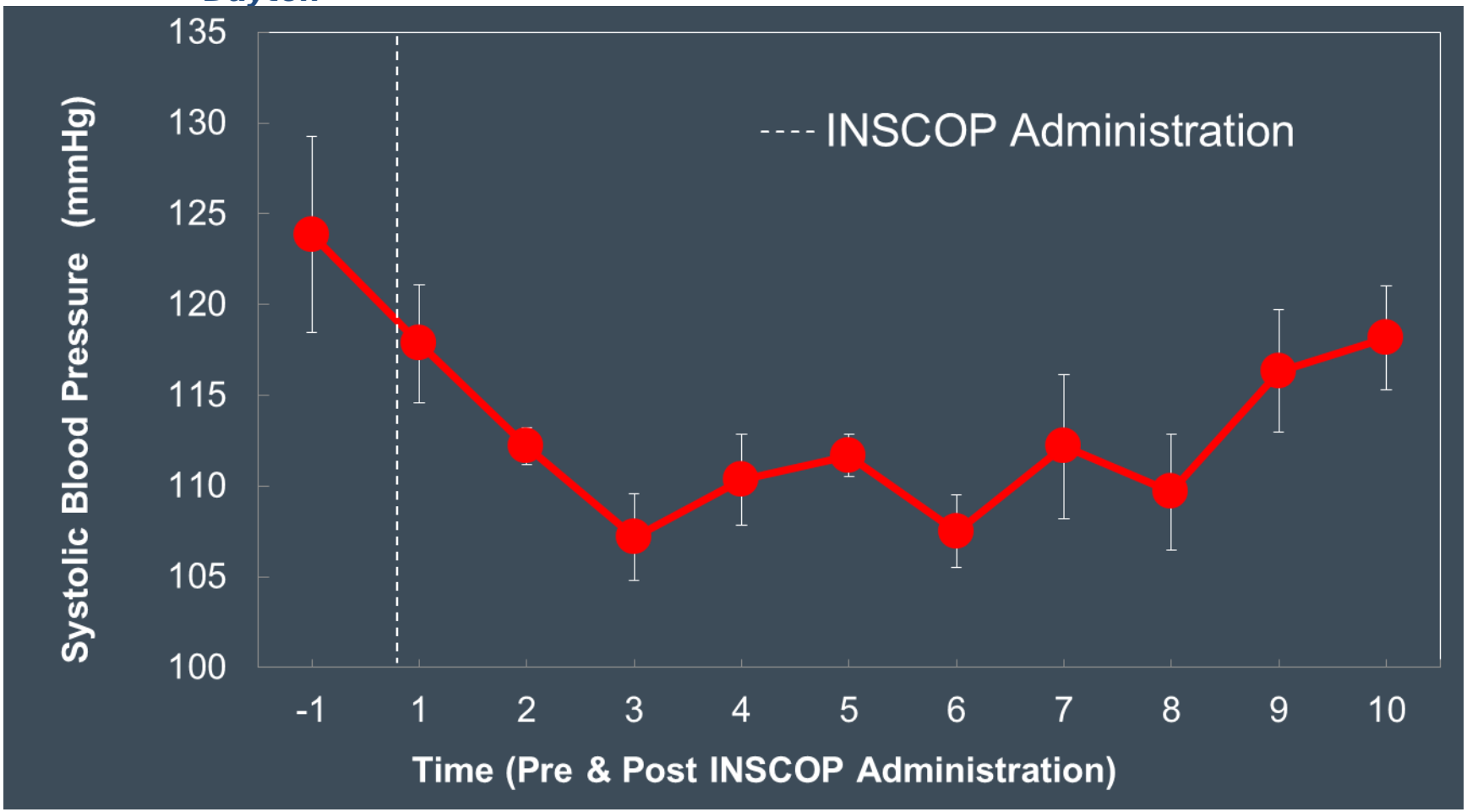

Pilot Study Results: ANAM

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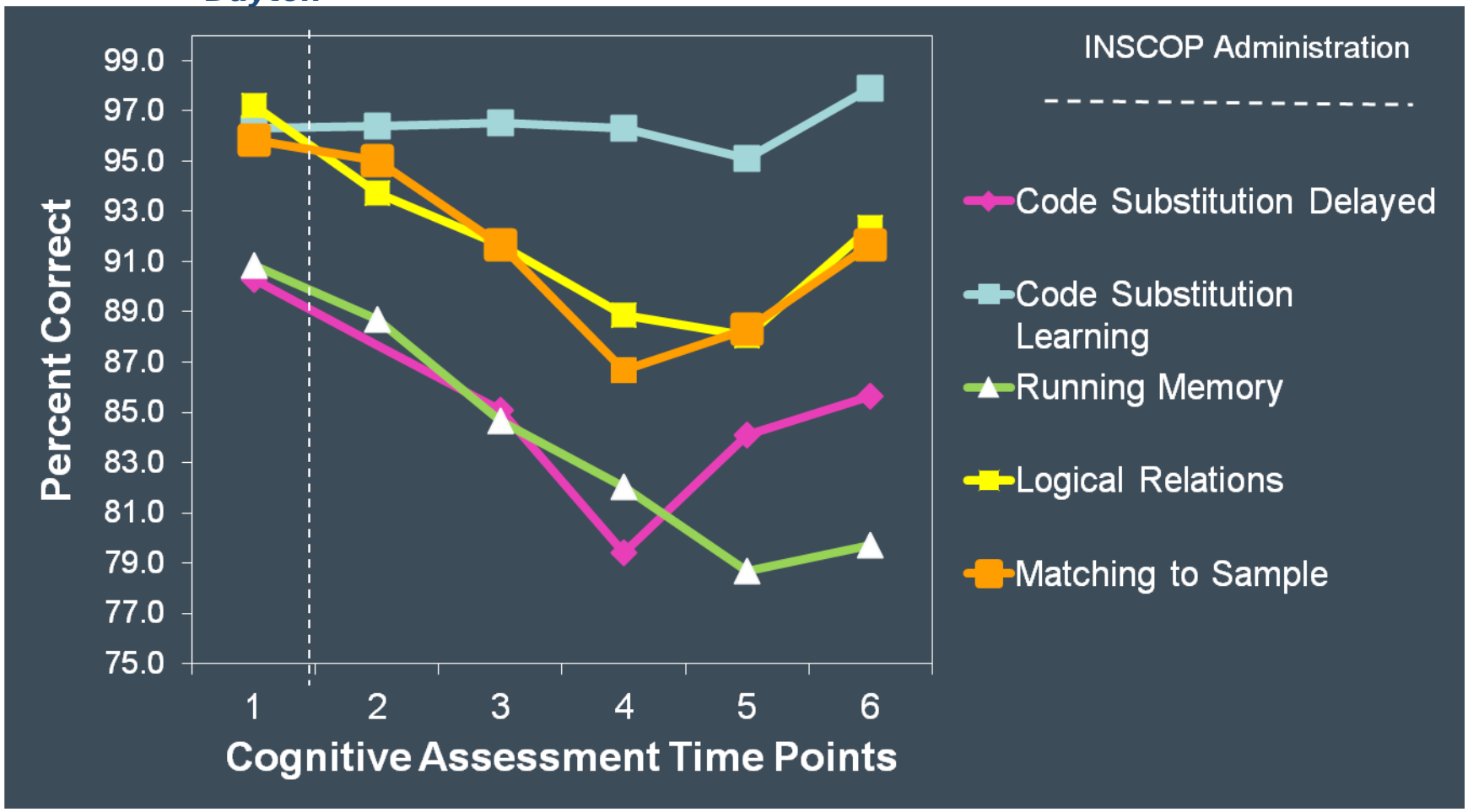

Preliminary Conclusions

- The preliminary results from the PK Pilot Study suggest that INSCOP spray may provide fast onset of action with consistent drug delivery at a lower than normal.
- These results will be verified in a FDA-approved Phase II clinical trial evaluating the pharmacokinetic and efficacy profiles of INSCOP spray for the treatment of MS.

Future Studies

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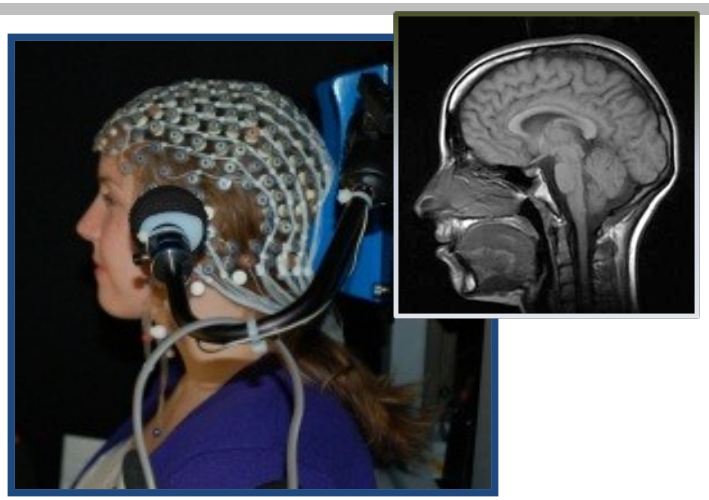

- INSCOP Spray Field Trial
  - FDA: Phase III Clinical Trial
    - Does it work in the fleet?
    - Does it work on real stimuli?
- MS Imaging Study
  - Controversy as to where MS response originates
  - Cross-over drug design with dense-array EEG imaging of hippocampal and surrounding areas
- Scopolamine Versus Promethazine Study
  - NASA swears by PROM; efficacious in space – what about normal gravity?

Future Studies

- MS Incidence Survey
  - Create a fleet-wide survey tool for anonymous reporting of MS symptoms and severity.
  - Identify the size of the effected population, specific at risk sub-populations, occurrence times (phase of flight, type of mission, sea state, etc.) and any MS interventions attempted.
  - Examine operational impact on performance.

Future Studies

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- Postural Instability: Detection of Individual Differences in Susceptibility
  - Why do some folks not get sick?
  - Engaging in functionally adaptive behavior has been shown to mitigate MS incidence.
  - Adopting a wider stance (e.g. feet 30cm apart) has been shown to reduce MS incidence both for visually induced MS and vestibular induced MS.
  - A wider stance is also beneficial for reducing morning sickness in pregnant women during the first trimester.

Sources: Stoffregen, Yoshida, Villard, Scibora, & Bardy, 2010; Stoffregen, Chen, Varlet, Alcantara, & Bardy, 2013; Yu, Chung, Hemingway, & Stoffregen, 2013

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